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10/030,332	02/15/2002	Yuji Ishihara	2599 USOP	5909

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EXAMINER	
CHANG, CELIA C	

ART UNIT	PAPER NUMBER
1625	

DATE MAILED: 09/16/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/030,332	ISHIHARA ET AL.	
	Examiner	Art Unit	
	Celia Chang	1625	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *18 June 2004* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *1-2, 5, 7-9, 11-16, 25-29, 32-36,38-41* is/are pending in the application.

4a) Of the above claim(s) *22-24* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1,2,5,7-9,11-16,25-29,32-36 and 38-41* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. This is a RCE of SN 010/030,332. A preliminary amendment and response filed by applicants dated June 18, 2004 have been entered and considered carefully. Claims 3-4, 6, 10, 17-21, 30-31, 33, and 37 have been canceled. Claims 22-24 remained withdrawn. Claims 1-2, 5, 7-9, 11-16, 25-29, 32-36, 38-41 are pending.

2. A restriction was made in the parent case and applicants have elected the subject matter, in the instantly amended claim 1, wherein R1-R2 forms homopiperidinyl. Please note that the election of group I claim 14 was *without* traverse or reasoning, and claim 14 is limited to piperidinyl compounds.

Claims 25 and 29 as now amended can be prosecuted together with the elected piperidinyl compounds to the extend of the piperidinyl compounds.

Claims 1-2, 11-16, 25-29, 32-36 and 38-41 being drawn to the piperidinyl compound are pending and examined.

3. The specification is objected to as containing NEW MATTER.

37 CFR 1.118. *Amendment of disclosure.*

(a) No amendment shall introduce new matter into the disclosure of an application after filing date of the application (§ 1.53(b)). All amendments to the specification, including the claims, and the drawings filed after the filing date of the application must conform to at least one of them as it was at the time of the filing of the application. Matter not found in either, involving a departure from or an addition to the original disclosure, cannot be added to the application after its filing date even though supported by an oath or declaration in accordance with § 1.63 or § 1.67 filed after the filing date of the application.

(b) If it is determined that an amendment filed after the filing date of the application introduces new matter, claims containing new matter will be rejected and deletion of the new matter in the specification and drawings will be required even if the amendment is accompanied by an oath or declaration in accordance with § 1.63 or § 1.67.

Support for amendment of page 9, paragraph 4 is said to be found in example 25. Applicants argued that the addition on page 9 is merely adding the species into the detailed

description. Please note that such addition is adding NEW MATTER to the specification for which no descriptive support can be found. Please note that in example 25, the compound is a benzylidinyl moiety substituted at 4-position of unsubstituted NR1R2=piperidine, when R3 is unsubstituted phenyl, E is trimethylene, G is CO, J is CH, Q is CH2, R is CH2, R4 is CH3,N-benzylidine which corresponds to the R4 group of the formula. This description does not support the amendment of page 9 where a general description with respect to the "optional substitution" on the aryl ring was concerned. While applicants can claim compound of example 25 by its structure or name, no support or antecedent basis that "generically" the aryl of the specification finds "description" of an benzylidinyl substituent.

Support for amendment of page 14, paragraph is said to be found at page 5 line 14 and example 9. Please note that the triflouroethyl of example 94 is on the N-benzyl corresponding to when NR1R2 is 4-benzylpiperidine, R3 is 3-chlorophenyl, E is trimethylene, G is CO, J is CH, Q is CH2, R is CH2, R4 is 2-trifluoromethyl phenyl. Therefore, no support for any umbrella extrapolation to substitution on the aryl moiety. The description on page 5 was on R4 is benzyl. While applicants can claim compound of example 94 by name or structure, no support or antecedent basis that "generically" the aryl of the specification can optionally be all substituted by "halo-substituted alkyl".

Support for amendment of page 17, paragraph 3 is said to be aim at addition of an embodiment where R3 is "aryl optionally having substituent" the substitutent is.....supported by examples 45 and 49. Please note that examples 45 and 49 supported compounds wherein NR1R2 is 4-benzylpiperidine, R4 is methyl, E is trimethylene, G is CO, J is CH, Q is CH2, R is CH2, R3 is triflouromethoxy or phenylmethosy. While applicants can claim example 45 or 49 by name or structure, no support or antecedent basis that "generically" all the aryl of the specification can optionally be substituted by "hydroxyl group optionally having substituent" To the extend that the scope of claims 1-2, 7-9, 11-16, 25-29, 32-36 and 38-41 with the term "optionally substituted" or substituents thereof, the claims would now included the above amendment of the specification, the claims are **rejected** under 35 USC 112 first paragraph as containing NEW MATTER. Removal of all NEW MATTER is required. In re Ressmussan 211 USPQ 325.

4. The rejection of claim 1 under 35 USC 112 second paragraph for the ambiguity of hydrocarbon moiety containing non-carbon or hydrogen structure is maintained for reason of record.

Applicants argued that this description is found on page 13 lines 6-34. Please note that at this particular section, it was found, hydrocarbon optionally substituted is referring "heterocyclic group optionally having a substituent" (line 15), therefore, what is the moiety? Which part is hydrocarbon which part is substituent? Dose the heterocycle is being considered hydrocarbon? The basis of ambiguity is found in reading the specification wherein no specific definition of "hydrocarbon" was given only examples (see specification p.7-8). The ambiguity of which is a substituent on what moiety is vary confusing. The ambiguity is self evidenced on the above new matter issues. Applicants are confused by whether the "terms" of the specification actually covers the species as exemplified and makes attempt to insert additional terms in the specification contradictory to the certified translated copies of priority document.

5. The rejection of claim 16 under 35 USC 112 second paragraph is changed to 35 USC 112 first paragraph in view of the amendment.

Claim 16 as amended now is *self conflicting* since a "pharmaceutical" composition must not be ineffective or toxic, the quantitative limitation of comprising a "therapeutically effective amount" must be incorporated to be consistent with the pre-amble.

6. The rejection of claim 15 under 35 USC 112 first paragraph for lacking adequate description on the scope "prodrug" is maintained. Please note that it was clearly delineated in the previous office action that no description as to target specific carrier, etc. prodrugs were found on page 26 lines 12-33. Applicants are urged to consult the textbook by Silverman (provided in previous office action) as to what one skilled in the art would considered being encompassed by the term "prodrug". MPEP §2111requires that the claims be interpreted by giving their broadest reasonable interpretation. If applicant's intended scope are those produrg modifications being limited to those as described on page 26 lines 12-33, then, it is recommended that the specific prodrugs found in the specification be incorporated in the claim.

7. The rejection of claim 28 under 35 USC 112 first paragraph is maintained for reason of record. The specific CCR5 antagonistic effective amount of the compounds in inhibiting HIV in spreading to uninfected cells as found on pages 106-108 does not provide enablement for the scope of the claims as suppressing all CCR5 receptor involved activities. Applicants are urged to consult the reference provided in the previous office action (CA 125) to the high unpredictability and limited understanding of chemokine receptor function in the art. In view of the documented high degree of unpredictability of chemokine receptor function, it is recommended that the specific inhibition of HIV infection of human peripheral blood mononuclear cells as described on page 2 be incorporated.

Claim 28 is rejected under 35 U.S.C. 112, first paragraph, i.e. "scope" of the claim lacks sufficient support, because the specification, while provided description and enablement that the compounds have activity for inhibition of HIV in spreading to uninfected cells, does not reasonably provide enablement for the *scope* of the instant claim as suppressing all chemokine receptor activity. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to operate the invention commensurate in scope with these claims.

Please note that the instant compounds being CCR5 chemokine receptor inhibitory does not offer any descriptive or enabling support for all chemokine receptor activity. It is well known in the art that chemokine receptor function is complexed and highly unpredictable (see Cohen et al. CA 125). While specific chemokine can link to a specific biological reaction, the mechanisms how chemokines (which is a kind of cytokine) function is very limited, thus, no extrapolation to broad application finds support in the art.

In addition, claims being drawn to mechanistic binding of receptors are considered reach-through claims. Reach through claims lacks descriptive support from the specification (See Baker Botts In Print attached) since such claim intended to cover the scope of future development for chemokine receptor/CCR5 functionality.

8. The rejections of claims 1-13, 15-16, 30-39 under 35 USC 103(a) over Kato or Kim in view of Caldwell, which are now applicable to the newly amended claims 1-2, 5, 7-8, 11-16,

25-29, 32-36,38-41 being drawn to the piperidinyl compounds are maintained for reason of record.

The claimed benefit of priority is denied because the certified translation verified that the invention as described in the priority document is not *the same invention* as the instant specification and claims. Particularly for example, the description of the instant specification on pages 4-5 are not found in the priority documents (compare translation p.9), the description on pages 9-10 are not found in the priority document (compare translation p.12), exhausted listing is not made but the examples described supra are evidence indicated that the instant specification and claims are not *the same invention* as the priority document.

The rejection of claims 1-2, 5, 7-8, 11-16, 25-29, 32-36,38-41 over Kato or Kim in view of Caldwell are maintained because the priority documents evidenced that there can be no granting of priority benefit.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

(A)

Claims 1-2, 5, 7-8, 11-16, 25-29, 32-36,38-41, are rejected under 35 U.S.C. 103(a) as being unpatentable over Kato et al. CA 134.

Determination of the scope and content of the prior art (MPEP §2141.01)

Kato et al. disclosed a homologous species of the claims to have melanin concentrating hormone antagonistic activity.

Ascertainment of the difference between the prior art and the claims (MPEP §2141.02)

Kato et al. disclosed all the elements of the claims **except** a species wherein R^2 is methyl for compound # 331756-17-3 was not exemplified. In the attached relevant pages, Kato generically taught that N-methyl is an optional choice for melanin concentrating hormone antagonist compounds as disclosed (see p.201 of 331756-17-3 and p. 281 example 202 N-methylated example).

Finding of prima facie obviousness—rational and motivation (MPEP§2142-2143)

One having ordinary skill in the art would find the instant N-methylated compounds of Kato prima facie obvious because not only the one methylated homologs are considered prima facie obvious (In re Doebel 174 USPQ 158) in the chemical compound art, it is explicitly guided by Kato's generic teaching together with example 202. One skilled in the art would be

motivated to prepared all the compounds generically taught by Kato and there is nothing unobvious in picking some among many (In re Lemin 141 USPQ 814) exemplified compounds with desirable attributes guiding one how to pick and choose among the genus for its known utility.

(B)

Claims 1-2, 5, 7-8, 11-16, 25-29, 32-36,38-41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kim et al. US 6,511,994 in view of Caldwell et al. US 6,136,827.

Determination of the scope and content of the prior art (MPEP §2141.01)

Kim et al. '994 disclosed compounds and compositions (col. 3 formula I, col. 27-32) encompassed the instant claims and a structurally very close species is disclosed at col. 98, line 55, example 42.

Ascertainment of the difference between the prior art and the claims (MPEP §2141.02)

Generically, Kim et al. '994 disclosed all the elements of the claims **except** a species anticipating the claims was no exemplified while example 42 at col. 98, line 55 is a homolog of the claims wherein R^3 is H instead of the claimed methyl.

Finding of prima facie obviousness—rational and motivation (MPEP§2142-2143)

One having ordinary skill in the art would find the instant claims which are N-methylated compounds of Kim '994 prima facie obvious because not only the one methylated homologs are considered prima facie structurally obvious (In re Doebel 174 USPQ 158) in the chemical compound art, it is taught by Kim '944 in the generic teaching. Further, in analogous art by Caldwell et al. '827 which taught similar piperidinyl CCR5 compounds, it was explicitly taught that N-methylation of an amido linker in such compounds is a desirable attributes for such compounds (see col. 22-23 amido compounds) **because** among all the compounds disclosed by Caldwell '827 (see col. 16-61), all amido or sulfonamido "N" is substituted by an alkyl. Such exclusive disclosure is suggestion to one skilled in the art that such attribute is desirable and would be successful in analogous compounds (In re Baird 29 USPQ2d 1550). Therefore one skilled in the art in possession of Kim '994 with example 42 have been provided with the suggestive guidance from Caldwell '827 to the picking and choosing of the methyl homolog among the generic R^2 of Kim et al.'994 to modify the unsubstituted species of Kim example 42.

9. This is a RCE of applicant's earlier Application No 10/030,332. Any new explanations for the same ground of rejection supra are necessitated by applicants amendments. All claims are drawn to the same invention claimed in the earlier application, and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the earlier application. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first

action in this case. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no, however, event will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Celia Chang whose telephone number is 571-272-0679. The examiner can normally be reached on Monday through Thursday from 8:30 am to 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner can be reached by facsimile at (703) 308-7922 with courtesy voice message supra.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1235.

Celia Chang
Primary Examiner
Art Unit 1625

OACS/Chang
Sept. 14, 2004